obviousness in any of the three assertions presented in the office action and outlined below.

§103 Rejections

*I. Claims 1-39 were rejected under 35 USC §103(a) as being unpatentable over Heible, et al., Recent Progress in the Pharmacotherapy of Diseases of the Lower Urinary Tract, **30**, 269S-198S (1995).*

It is important to note that Heible discusses two separate and distinct diseases, namely benign prostatic hypertrophy (BPH) and urinary incontinence (UI). See, page 271s, 1st paragraph.

Heible discusses BPH (section 2, pages 272s to 283s) and the use of α-adrenoceptor antagonists in that connection. In addition, Heible teaches that long term therapy with α-antagonists does not produce a reduction in prostatic volume (page 282s, 3rd paragraph, 1st line); whereas, 5- α-reductase inhibitors do show such an effect (page 283s, 2nd paragraph, lines 1-2). Although a combination of α-adrenoceptor antagonists with 5- α-reductase inhibitors is taught, the only other combination treatment alluded to in the reference is the combination of an α_1-adrenoceptor antagonist with an androgen receptor antagonist. No further combinations are suggested.

Heible also discusses UI (section 3, pages 284s to 293s) and the use of muscarinic antagonists in that connection; however, there is no discussion or suggestion for use of muscarinic antagonists for treating BPH. One skilled in the art would understand these diseases to be separate and distinct, and would therefore not consider the use of muscarinic antagonists in connection with treating BPH. The Examiner's assertion that it is obvious to combine the two compositions is incorrect, because it is not taught or suggested by the reference that each composition is useful for the same purpose.

Furthermore, Heible teaches that muscarinic antagonists are widely used for the treatment of urge incontinence and also warns that "both voluntary and involuntary contractions of the bladder are inhibited by these agents. Urinary retention may therefore result, especially in patients with outlet obstruction" (page 287s, 1st paragraph, lines 3-6). As mentioned in the description of the present application, bladder outlet obstruction results from BPH (page 1, lines 14-16 and 23). Based on the teachings of Heible, one skilled in the art would understand that muscarinic antagonists would not be suitable for the treatment of BPH because use of such compounds would result in

exacerbation of the symptoms already caused by BPH. Hence, Heible teachs away from the use of muscarinic antagonists for treating BPH. As a result, Examiner has failed to establish a prima facie case of obviousness based on the teachings of Heible and the rejection must be withdrawn.

II. Claims 1-39 were rejected under 35 USC 103(a) as being unpatentable over Ukimura, "Effects of Intravesically administered anticholinergics, beta-adrenergic stimulant and alpha-adrenergic blocker on bladder function in unanesthetized rats," Tohoku Journal of Experimental Medicine, 170(4), 251-260 (1993).

Ukimura discusses the use of various agents for the treatment of bladder disorders, in particular detrusor hyperreflexia (see, abstract - last two lines). BPH is not a bladder disorder, it is a condition of the prostate which causes urethral resistance. Therefore, the fact that this study shows that the α-adrenoceptor antagonists and muscarinic antagonists mentioned are useful for the treatment of spontaneous bladder contraction would not suggest to one skilled in the art of their utility in treating BPH. Indeed, as discussed earlier, the skilled artisan would understand that muscarinic antagonists cause urinary retention due to inhibition of contractions of the bladder. Therefore, one of skill in the art would be dissuaded by this reference to use such agents in the treatment of BPH. Furthermore, there is no teaching that an advantageous effect would be seen as a result of the combination of any of the agents mentioned and thus one skilled in the art would not be motivated to make such a combination.

III. Claims 1-28 were rejected under 35 USC §103(a) as being unpatentable over Cilluffo, et al., "Synergistic receptor-activated calcium increases in single nonpigmented epithelial cells," Investigative Opthalmology and Visual Science, 39(8), 1429-1435 (1998).

Cilluffo discusses changes in the intracellular free calcium ion concentration in connection with cellular function. It is taught that such changes are relevant to the pharmacologic responses of ocular epithelia. Clearly, this reference is not related to the same field as the present application. One skilled in the art of BPH would not look to the field of ophthalmology for teachings or suggestions. Even if one skilled in the art was aware of this reference, the reference does not teach or suggest combining α-adrenoceptor antagonists and muscarinic antagonists.

The reference simply teaches that certain receptors produce large synergistic increases in calcium ions when stimulated in combination and, as an example of this, it discloses that simultaneous muscarinic and adrenergic activation results in a large synergistic increase of calcium ions. In addition to specific agonists, muscarinic and adrenergic antagonists were used to classify the receptors involved in the response of the cells. Although the reference states that the response could be blocked by either a specific alpha2-antagonist or a muscarinic antagonist, it does not imply that the two are combined. Instead, the antagonists were used separately as a tool to determine the identity of the receptors involved in the cells. (see, page 1431, 2nd column, 1st full paragraph). Clearly, the reference does not teach or suggest that such antagonist agents should be combined for a pharmacologic treatment. The reference teaches the synergistic effects of combining agonist agents and not antagonist agents. Therefore, Cilluffo does not teach or suggest combining α-adrenoceptor antagonists and muscarinic antagonists. A copy of the full article is attached hereto for Examiner's convenience.

Based on the foregoing arguments, Applicants respectfully submit that Claims 1-39 are in condition for allowance.

Respectfully Submitted:

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